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(71) Applicants
Roussel-Uclaf,
35 Boulevard des
Invalides, Paris 7ème,
France
(72) Inventors
Paul Zeitoun
Patrick Brisard
(74) Agents
Frank B. Dehn & Co.,
Imperial House,
15/19 Kingsway,
London WC2B 6UZ

(54) **Delayed-release tablets for disintegration in the colon**

(57) Delayed-release pharmaceutical tablets for disintegration in the colon comprise a compressed tablet core containing a pharmaceutically active agent, the said core being coated successively with: a) a first coating layer comprising a film-forming agent (e.g. ethyl cellulose) which does not deteriorate in neutral or alkaline medium, together with microcrystalline cellulose, and b) a second coating layer comprising an enteric coating agent.

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SPECIFICATION

Compressed tablets for disintegration in the colon

This invention relates to new compressed tablets adapted for disintegration in the colon, as well as to a process for preparing them.

By compressed tablets adapted for disintegration in the colon is meant herein compressed tablets of which the centre containing the active principle disintegrates substantially specifically in the colon.

In French Patent Specification No. 1,591,602 are described pharmaceutical dosage forms for oral administration, in which the active principle remains substantially protected from the digestive juices of the stomach and of the small intestine, whereby practically all the active ingredient is released in the colon. In these pharmaceutical forms the active principle is finely divided and surrounded with a resin.

These forms, however, possess a number of disadvantages. The duration of the gastro-intestinal transit varies considerably from one individual to another and according to the size of meals it can range from about twelve hours to more than twenty-four hours. Given that the dissolution of the resin covering the active principle is proportional to time, release of the latter in the colon is rather uncertain. In addition, it is difficult to coat the active principle homogeneously.

Attempts have, therefore, been made to find a technique other than simple dissolution which enables total specificity of release of the active principle at the level of the colon to be obtained.

It is known that the digestive tract of man is devoid of specific enzymes permitting the digestion of cellulose; however bacteria existing in the human colon have the ability to digest cellulose. We have found that this fact may be used to prepare compressed tablets which exhibit good specificity of release of the active principle in the colon by coating the active principal with a layer which includes microcrystalline cellulose.

Thus according to one feature of the present invention we provide compressed tablets adapted for disintegration in the colon comprising a centre containing the active principle, the said centre being covered successively:

a) with a first coating layer comprised of a film-forming product which does not deteriorate in neutral or alkaline medium and of microcrystalline cellulose and

b) with a second coating layer comprised of an enteric coating agent.

The microcrystalline cellulose may, for example, be that sold under the name of Rehocel (Rettenmaier), Avicel PH (American Viscose Division), Avicel RC (Lehmann and Voss) or Lintenspuver LH 330 (Rettenmaier).

The enteric coating agent may, for example, be cellulose acetylphthalate, hydroxypropylmethylcellulose phthalate, benzophenyl salicylate, cellulose acetosuccinate or copolymers of styrene and of maleic acid. Particularly preferred as enteric coating agent is cellulose acetylphthalate.

Among the film-forming products which do not deteriorate in neutral or alkaline medium may preferably be considered ethyl cellulose.

In order to provide fine and solid coating films, the coating layers advantageously additionaly contain one or more plasticisers. The plasticisers may for example, be selected from diethyl phthalate, dibutyl phthalate, propylene glycol and castor oil, the use of diethyl phthalate, dibutyl phthalate and/or propylene glycol being preferred.

Particular compressed tablets according to the invention which may be mentioned are those wherein the first coating has a mass of from 0.5% to 10% of that of the centre and the first coating contains from 30% to 80% by mass of microcrystalline cellulose.

Also preferred are compressed tablets wherein the enteric coating agent has a mass of from 2% to 10% of that of the centre.

According to a further feature of the present invention there is provided a process for preparing the new compressed tablets as defined above, which comprises coating centres containing the active principle by spraying thereon a solution of a film-forming product which does not deteriorate in neutral or alkaline medium and of microcrystalline cellulose in a solvent; drying the said coated centres; and then spraying a solution of an enteric coating agent in a solvent onto the dried coated centres and drying. If desired the solution of the film-forming product and cellulose and/or the solution of the enteric coating agent may additionally contain one or more plasticisers.

The film-forming agent and, if present the plasticiser(s) may be put into solution according to methods known *per se*, for example in methyl, ethyl or isopropyl alcohol, in acetone, ethyl acetate or ethylene chloride or in a mixture of these solvents. Coating can, for example, be carried out in a tumbler or by spraying onto the compressed tablets in suspension in air. The use of a tumbler is however preferred.

The compressed tablets, which form the subject of the present invention, confer a delay effect upon the active principle by localising its release to the colon. These compressed tablets are thus of particular interest for giving medicaments where delayed release is desirable such as e.g. using barbiturates, amphetamine and aspirin. In addition, a colon-localised effect is also often sought, for example, in the treatment of certain parasitic complaints such as colic amoebiases.

Particular medicinal active principles which may be mentioned for use in the compressed tablets of the present invention include, for example, thos where a delayed release and/or a colon-localised release is desirable such as corticoids, anti-inflammatory agents, antibacterial agents and antibiotics.

It will be appreciated that the compressed tablets, of the present invention can if desired contain conventional adjuvants such as wetting agents, colouring agents or diluents, in the centres, and/or colouring agents or substances capable of protecting the active principle against the light, in the coatings.

The following non-limiting Examples serve to

illustrate the present invention.

Example 1:

Preparation of neomycin compressed tablets.

500 centres, each weighing 400 mg and containing 200 mg of neomycin sulphate, are introduced into a glass tumbler rotating at 30 revolutions/minute, and are sprayed for 40 minutes, under a pressure of 0.3 bar, at ambient temperature, with 22.5 ml of a solution of ethyl cellulose comprising:

- ethyl cellulose ..... 60 g
- dibutylphthalate ..... 25 g
- propylene glycol ..... 15 g
- isopropanol ..... 650 ml
- ethanol ..... 650 ml

with which was mixed microcrystalline cellulose (Avicel PH 101) ..... 1.25 g

then left to dry for one night under vacuum. 500 coated centres each weighing on average 403 mg are thus obtained. These coated centres are then sprayed, for one hour, under a pressure of 0.1 bar, at ambient temperature, with 320 ml of a solution comprising:

- cellulose acetylphthalate ..... 50 g
- diethylphthalate ..... 5 g
- isopropanol ..... 500 ml
- ethyl acetate ..... 500 ml

then left again for one night under vacuum. 500 coated compressed tablets are obtained, each weighing on average 428 mg.

Example 2:

Preparation of prednisolone compressed tablets.

500 centres each weighing 398 mg doses and containing 5 mg of prednisolone are introduced into a glass tumbler, rotating at 40 revolutions/minute, and are sprayed for 35 minutes, under a pressure of 0.2 bar, at ambient temperature, with 45 ml of a solution of ethyl cellulose comprising:

- ethyl cellulose ..... 60 g
- dibutylphthalate ..... 25 g
- propylene glycol ..... 15 g
- isopropanol ..... 650 ml
- ethanol ..... 650 ml

with which was mixed microcrystalline cellulose (Avicel PH 101) ..... 5 g

and to which were added 45 ml of a mixture in equal parts of isopropanol and ethyl alcohol. Partial drying is then carried out in fresh air, then the coated centres are left to dry for one night under vacuum. 500 coated centres are thus obtained, each weighing on average 411 mg. These coated centres are then sprayed for one and a half hours, at ambient temperature, under a pressure of 0.1 bar, with constant drying in fresh air, with 320 ml of a solution comprising:

- cellulose acetylphthalate ..... 50 g
- diethylphthalate ..... 5 g
- isopropanol ..... 500 ml
- ethyl acetate ..... 500 ml

then left again to dry for one night under vacuum. 500 coated compressed tablets are obtained, each weighing on average 444 mg.

Examples 3, 4, 5, 6, 7:

Preparation of barium sulphate compressed tablets.

Work is carried out according to the method described in Example 2. The centres each weigh on average 398 mg and contain 100 mg of barium sulphate.

	Examples				
	3	*4*	*5*	*6*	*7*
Ethyl cellulose solution	29.8ml	34.2ml	37.0ml	40.3ml	44.2ml
Microcrystalline cellulose	2.72 g	2.87 g	2.90 g	3 g	3 g
Isopropanol/ ethanol mixture	29.8ml	34.2ml	37.0ml	40.3ml	44.2ml
Final weight of the compressed tablet	444mg	438mg	438mg	440mg	434mg

CLINICAL STUDY:

A) – *Study protocol.*

The disintegration of the compressed tablets of Examples 3, 4, 5, 6 and 7 was tested, in man. The compressed tablets contain barium sulphate. They are thus visible on a radiographic control.

With dinner (19.30 hours) and the next day with breakfast (07.00-08.00 hours) a compressed tablet was given to the patient, that is 2 in all.

A radiograph of the abdomen was taken between 14.00 hours and 15.00 hours, that is about 19 and 7 hours respectively after the oral dose.

It was possible to observe:

1 – *The state of disintegration* of the compressed tablets which is expressed in the following manner:

– *whole* for a compressed tablet of preserved outline and density,

– *eaten away* for a compressed tablet slightly changed on its density and outline,

– *emptied* for a compressed tablet of which only the still-locatable shell is visible and

– *disintegrated* for an n-visible compressed tablet.

Since none of the patients had motor diarrho a, the non-visible compressed tablets were in reality disintegrated and not removed in the stools.

2. – *The location of the compressed tablets* defines the organ in which they are visible : three were located in the stomach and several in the small or in the large intestine.

B) – *Results.*

These are detailed in the summary of observations appearing h reinafter.

The following *conclusions* can be drawn:

a) The compressed tablets given the day before in the evening, that is to say 19 hours before the radiograph are all disintegrated:

b) the compressed tablets which are in the small intestine are all whole;

c) the compressed tablets which are seen in the colon are rarely whole.

OBSERVATIONS

Compressed tablets of Example 3

FIRST COMPRESSED TABLET Condition and location	*SECOND COMPRESSED TABLET* Condition and location
ADD ... DISINTEGRATED	WHOLE. CAECUM
FRE ... DISINTEGRATED	WHOLE. RIGHT CORNER OF THE COLON
DEL ... DISINTEGRATED	DISINTEGRATED
COU ... DISINTEGRATED	DISINTEGRATED
KUN ... DISINTEGRATED	DISINTEGRATED
MAS ... DISINTEGRATED	DISINTEGRATED
KUL ... DISINTEGRATED	DISINTEGRATED
SAR ... DISINTEGRATED	WHOLE. STOMACH
BRU ... DISINTEGRATED	WHOLE. RIGHT CORNER OF THE COLON

Compressed tablets of Example 4

FIRST COMPRESSED TABLET Condition and location	*SECOND COMPRESSED TABLET* Condition and location
KER ... DISINTEGRATED	DISINTEGRATED
GOD ... DISINTEGRATED	DISINTEGRATED
HUR ... DISINTEGRATED	DISINTEGRATED
RYL ... DISINTEGRATED	DISINTEGRATED
DIR ... DISINTEGRATED	WHOLE. SMALL INTESTINE
ROY ... DISINTEGRATED	WHOLE. SMALL INTESTINE
BOU ... DISINTEGRATED	WHOLE. SMALL INTESTINE
NGU ... DISINTEGRATED	DISINTEGRATED
FEH ... EMPTIED. CAECUM	WHOLE. SMALL INTESTINE

Compressed tablets of Example 5

FIRST COMPRESSED TABLET Condition and location	*SECOND COMPRESSED TABLET* Condition and location
CAM ... DISINTEGRATED	DISINTEGRATED
LAM ... DISINTEGRATED	DISINTEGRATED
KOC ... DISINTEGRATED	WHOLE. RIGHT CORNER OF THE COLON
LOU ... DISINTEGRATED	WHOLE. CAECUM
SAL ... DISINTEGRATED	WHOLE. RIGHT CORNER OF THE COLON
LAS ... DISINTEGRATED	WHOLE. RIGHT CORNER OF THE COLON
PON ... DISINTEGRATED	DISINTEGRATED

Compressed tablets of Example 6

FIRST COMPRESSED TABLET Condition and location	*SECOND COMPRESSED TABLET* Condition and location
DUR ... CAECUM. EATEN AWAY	WHOLE. SMALL INTESTINE
CHA ... DISINTEGRATED	WHOLE. SMALL INTESTINE
DEL ... DISINTEGRATED	WHOLE. SMALL INTESTINE
AIR ... DISINTEGRATED	DISINTEGRATED
DER ... EMPTIED. RIGHT CORNER OF THE COLON	WHOLE. SMALL INTESTINE
HUR ... DISINTEGRATED	DISINTEGRATED
BEN ... EMPTIED. RIGHT CORNER	WHOLE. SMALL INTESTINE

Compressed tablets of Example 7

FIRST COMPRESSED TABLET Condition and location	*SECOND COMPRESSED TABLET* Condition and location
MER . . . DISINTEGRATED	EATEN AWAY. SMALL INTESTINE
FRA . . . DISINTEGRATED	DISINTEGRATED
BER . . . DISINTEGRATED	WHOLE. SMALL INTESTINE
REM . . . DISINTEGRATED	WHOLE. STOMACH
GON . . . DISINTEGRATED	WHOLE. RIGHT CORNER
JOE . . . DISINTEGRATED	WHOLE. STOMACH
NEP . . . EMPTIED. RIGHT CORNER OF THE COLON	WHOLE. CAECUM
LEG . . . DISINTEGRATED	DISINTEGRATED
GAU . . . DISINTEGRATED	DISINTEGRATED

CLAIMS

1. Compressed tablets adapted for disintegration in the colon comprising a centre containing the active principle, the said centre being covered successively:
a) with a first coating layer comprised of a film-forming product which does not deteriorate in neutral or alkaline medium and of microcrystalline cellulose and
b) with a second coating layer comprised of an enteric coating agent.

2. Compressed tablets as claimed in claim 1 wherein at least one of the coating layers additionally contains one or more plasticizers.

3. Compressed tablets as claimed in claim 1 or claim 2 wherein the first coating has a mass of from 0.5% to 10% of that of the centre, and the first coating contains from 30% to 80% by mass of microcrystalline cellulose.

4. Compressed tablets as claimed in any preceding claim wherein the film-forming product is ethyl cellulose.

5. Compressed tablets as claimed in any preceding claim wherein the enteric coating agent is cellulose acetylphthalate.

6. Compressed tablets as claimed in any preceding claim wherein the enteric coating agent has a mass of from 2% to 10% of that of the centre.

7. Compressed tablets as claimed in any preceding claim wherein the plasticisers are selected from diethyl phthalate, dibutyl phthalate and propylene glycol.

8. Compressed tablets as claimed in claim 1 substantially as herein described.

9. Compressed tablets substantially as herein described in any one of Examples 1 to 7.

10. A process for preparing compressed tablets as claimed in claim 1 which comprises coating centres containing the active principle by spraying thereon a solution of a film-forming product which does not deteriorate in neutral or alkaline medium and of microcrystalline cellulose in a solvent; drying the said coated centres; and then spraying a solution of an enteric coating agent in a solvent onto the dried coated centres and drying.

11. A process as claimed in claim 10 wherein the coating is carried out in a tumbler.

12. A process as claimed in claim 10 or claim 11 wherein the solution of the film-forming product and cellulose and/or the solution of the enteric coating agent additionally contain one or more plasticisers.

13. A process for the preparation of compressed tablets as claimed in claim 1 substantially as herein described.

14. A process for the preparation of compressed tablets as claimed in claim 1 substantially as herein described in any one of Examples 1 to 7.

15. Each and every novel method, process, composition and product herein disclosed.

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